



# Why is Healthy Donor Tissue So Important for Cell and Gene Therapies?

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## INTRODUCTION

Public discourse on cell and gene therapy is focused on novel approaches to long-established procedures such as bone marrow transplants, as well as on truly innovative treatments such as cancer immunotherapy and stem cell therapy for autoimmune disorders and other serious ailments. Positive clinical trial results and the demonstrated success of advanced therapies such as Kymriah® and Yescarta® are fueling a sense of excitement on what could be accomplished with these medicines—and driving a significant increase in the number of cell therapies in the clinical trial pipeline. As of last year, there were nearly 300 different cell and gene therapies in development, and that number is on target to grow. [1]

At the same time, new regulatory approval pathways are expediting clinical testing for promising new drugs that meet specific regulatory criteria and milestones. These advanced therapies receive an increased level of regulatory agency feedback and may be able to gain expedited approval, in certain

cases after only a single pivotal clinical trial. As a direct consequence, apheresis clinics and cell collection centers are facing an increasing demand for cell therapy starting materials. At HemaCare, we recognize that sourcing this starting material relies on human donors and that access to those donors can be limited by the size and diversity of a given donor network.

While necessary for autologous cell therapy treatments, patient-sourced disease-state material is understandably limited in quantity and availability. Even when such material is available, the collected cells are usually significantly compromised by the health of the patient. Healthy donor material, by contrast, is more consistently available and often a better source for high-functioning target cells. In fact, understanding the impact of healthy donor starting material is key to planning for successful commercialization of cell therapy products.

*“The newly thriving clinical cell therapy market is leading to a greater demand for apheresis driven technologies. Ensuring high-quality starting material means focusing on both optimizing therapeutic cell yield and maintaining peak therapeutic potency.”*

*-Dr. Dominic Clarke, Global Head of Cell Therapy, HemaCare Corporation*

## **THE NEED FOR HEALTHY DONOR CELLS**

Allogeneic therapies use healthy donor material both for process development and patient treatment. Sourcing cell therapy starting material from healthy donors has the obvious advantage of allowing for greater accessibility compared to disease-state material. Since cells collected from healthy donors are not impacted by disease, they also provide a more biologically relevant functional profile for assay development and quality assessments.

Autologous therapies, on the other hand, use a person’s own stem or immune cells to help fight disease while minimizing the risk of triggering a serious immune response or an accidental disease transmission. These dangers are real and potentially life-threatening. Autologous therapies are also designed to precisely match therapy to patient, allowing for a “personalized” approach to medicine. Nevertheless, in this modern age of breakthrough therapies and rapidly evolving clinical pipelines, there is a strong need for consistent, high-quality donor material that simply can’t be filled by patient donations.

Due to the limited availability of patient-derived source material, even autologous therapies generally use healthy donor material during development in order to develop robust and well-characterized methods of production. In fact, [HemaCare](#) provided healthy donor material throughout the development processes for both Kymriah® and Yescarta®, the world’s first two autologous CAR-T therapies. This material was necessary for process development, as well as for carrying out comparability runs. Healthy donor material is also needed to develop biologically relevant assays for quality control testing. If a patient is too sick to donate, it may be necessary to use an HLA-matched healthy donor for therapeutic treatment as well.

## **DISEASE IMPACTS CELL THERAPY STARTING MATERIAL**

Disease impacts the number, composition, and quality of progenitor cells and immune cells present in a patient’s circulation. Diseases like leukemia are a case in point. The disease is defined by the

overabundance of immature or abnormal white blood cells. These cells, commonly known as “blast” cells, suppress the production of normal cells and cause increasingly dangerous symptoms like fatigue, weight loss, frequent infections, and easy bleeding or bruising. A person suffering from leukemia basically needs to eliminate their own faulty immune cells and reboot their immune system with healthy cells.

CAR-T cell therapy uses the patient’s own immune cells for this process. T cells are collected via apheresis, then genetically modified to include the presence of an antigen engineered to recognize a protein specifically found on the surface of cancer cells. The modified immune cells are expanded and re-introduced into the patient, where they will hopefully be able to recognize and destroy the abnormal cancer cells. The successful clinical trial of this therapeutic technique, despite some serious early setbacks, eventually led to the approval of the world’s first CAR-T cell therapies. [2]

Those approvals have proven to be the tip of the iceberg. Successive generations of T cell therapies are now proceeding through the clinical trial pipeline, as researchers seek to improve upon the efficacy and safety of the original technique or develop similar immune cell-based strategies.

Ironically, the remarkable clinical success of CAR-T cell therapy runs the risk of leading to a bottleneck in the commercialization process. Sourcing adequate quantities of donor material is proving difficult, as cell collection centers and hospital apheresis units struggle to keep up with demand. T cell therapy manufacturers commonly use healthy donor apheresis products as starting material for process development to circumvent the fact that disease-state material is unreliable in terms of adequate therapeutic cell counts, composition, and availability. Healthy donors are matched to the intended patient as closely as possible in terms of tissue type, age, gender, and other physiological and demographic criteria, and can provide valuable insight into the functional differences between healthy donor cells and disease-state cells.

## **LIMITATIONS OF AUTOLOGOUS CAR-T THERAPIES**

While CAR-T cell immunotherapy is a powerful tool against cancer, it does have obvious drawbacks. Not all patients are able to safely donate immune cells for their treatment, and patient cell collection may not contain an adequate number of healthy immune cells to proceed with therapy. This puts the patients who need treatment most at the highest risk.

Autologous therapies, while wonderful for individual patients, are difficult to scale up to a larger population. T cells and other therapeutic immune cells cannot be indefinitely expanded without risking losses in therapeutic efficacy or other detrimental changes due to cellular senescence. Inadequate therapeutic cell numbers can lead to failed manufacturing runs and other delays. Perhaps most importantly, cancer is a very unpredictable disease. Treatment tailored to one patient may not work for the next, and patient-derived starting material always carries some risk of contamination with cancer cells. Autologous therapies are also difficult to scale up in terms of supply and demand; patient-derived T cells are not always available when they’re needed.

The answer, for many pharmaceutical researchers, is to develop an allogeneic version of CAR-T therapy manufactured using healthy donor cells. [3] On the surface, this can seem counter-intuitive, since the reason the healthcare industry uses autologous therapies is to avoid issues of donor tissue rejection and dangerous immune reactions like graft-vs-host disease. Ultimately, however, the goal of an “off-the-shelf” T cell therapy makes allogeneic CAR-T cells a worthy prospect.

## DEVELOPING ALLOGENEIC CAR-T CELLS

Allogeneic cell therapies are not limited to use by a single patient, and sourcing donor material for process development and treatment is simpler. Because the source material is coming from healthy donors, it is easier to optimize therapeutic cell yield, reducing variability and minimizing manufacturing delays.

Immune response issues are more difficult to address, but not impossible. CAR-T cells derived from healthy donors that have been HLA-matched to the patient are less likely to cause a dangerous immune reaction. While this type of therapy is not “off-the-shelf”, it does alleviate sourcing, manufacturing, and quality control issues.

Other methods of avoiding dangerous immune response are under investigation. Regulatory T cells can be modified to help temporarily mitigate an overcharged immune response. Gene-edited versions of healthy donor CAR-T cells are being developed that can reduce or knock out TCR receptor driven graft-vs-host disease. Within a few short years, it may well be possible to create “universal” CAR-T cells that can be used for any patient. The possibility of off-the-shelf CAR-T cell treatment would revolutionize the current state of cancer immunotherapy.

## DONOR NETWORKS AND SOURCING

Donor accessibility is unquestionably key to a [successful clinical trial](#). Cell therapy developers need access to a large diverse pool of reliable donors as different drug candidates move forward from preclinical research to clinical trial and through to commercialization. Clinical trials for autologous cell therapies need access to patient-derived apheresis material. At the same time, however, developing a robust process for manufacturing any cell therapy, including an autologous therapy, requires access to a wide range of different donor types of varying characteristics.

Access to recallable donors is often critical to clinical trial progress. For over 40 years, HemaCare’s expertise in donor recruitment and active maintenance of good donor relationships has been crucial to building the industry’s largest network of high-quality, reliable, and responsive donors. Recallable donors help support sourcing demands for allogeneic therapies and autologous process development. Cryopreserving donor material is also a good way of building inventory from selected donors in order to have that material on hand at need. This is particularly pertinent to late-stage clinical trial scale-up, when the need to go back and identify new donors meeting the appropriate screening criteria can mean lengthy delays. HemaCare’s large, diverse donor pool increases the odds of finding the right donor or donors within a satisfactory time frame, an issue which can be crucial for a waiting patient.



### Donor Recruitment

Dedicated team screens 100's of new donors monthly adding to multiple donor pools based on qualifying criteria.



### Donor Nurturing

Continuous follow up to advise potential donors on positive habits and practices to maximize donation yield.



### Donor Safety

Keeping in mind donor comfort and safety, HemaCare has strict guidelines limiting the total blood volume processed and in turn the time a donor is on the bed.

## **QUALITY IS KEY**

Starting material quality is also critical. Only high-quality starting material can make a high-quality product. Variability is always a factor where cell therapy is concerned, but steps can certainly be taken that limit that variability.

HemaCare's cell collection methods focus on a balance between yield and purity. Although there is certainly a focus on optimizing cell yield, there is a misconception in the industry that lower yield signifies a lower quality product. Large numbers of contaminating cell types can complicate cell isolation and separation processes, while higher flow rates can damage fragile cells. More conservative flow rates and collection volumes often yield a higher ratio of healthy therapeutic cells per donated unit, resulting in better efficacy downstream. The ability to recall unique donors, and access to a preferred donor pool, can reduce variability. It can also help ensure availability and security of supply as a therapy progresses from clinical trial to commercialization.

Choosing the right donor network is crucial to the overall development process since it will dictate foundational aspects of the final product such as the variety, consistency, sourcing reliability, cell collection and isolation methods, and quality oversight.

## **CLOSING REMARKS**

Beginning with consistent and reliable starting material enables pharmaceutical companies to develop a manufacturing process that is best suited to account for the requirements of scale and for the potential variability encountered. Healthy donor material is critical to this process. It is by nature more consistently available, and a better source of high-functioning therapeutic cells. HemaCare's longstanding goal of supporting innovative medical applications is reflected in its expansive apheresis network of recallable healthy donors. Access to this network improves the chances of finding donors with specific genetic and medical backgrounds who are capable of fulfilling stringent exclusion and inclusion criteria for preclinical and clinical studies within an acceptable timeframe.

Cell therapy providers need to plan the manufacturing process with the end goal in mind, and access to healthy donor material is one of the most important aspects of that planning.

## **REFERENCES**

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